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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/646,479	VERMA ET AL.	
	Examiner	Art Unit	
	Marcia S. Noble	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-7,9,10 and 15-18 is/are pending in the application.

4a) Of the above claim(s) 8 and 11-14 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-7,9,10 and 15-18 is/are rejected.

7)☐ Claim(s) 8 and 11-14 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-18 are pending and under consideration.

Claim Objections

2. Claims 8 and 11-14 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only and/or can not depend from other multiple dependent claims. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits and are withdrawn from consideration.

It is notes the claim 15 does not recite any specific claim number but does recite "according to a process comprising or including a process as defined in any preceding claim." This potentially makes this claim a multiple dependent claim. However, without reference to a specific method, the product will be examined with minimal reference to any specific method.

Claim Rejections - 35 USC § 101 and §112, 2nd paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claim 18 is provides for the use of cloned pigs, for organ production, or oocyte and embryo production, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass.

A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 18 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claims 15-18 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 15-18 are drawn to "cloned pigs". While there is an apparent hand of man, a "clone" can not be distinguished from any naturally occurring pig or animal.

Claim 16 is also rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 16 is drawn to the progeny of a cloned pig. While there is an apparent hand of man, a "clone" can not be distinguished from any naturally occurring pig or animal. Furthermore, in the production of progeny from the cloned pig, wild type pigs will be generated in the matings.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1 and 5 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 13, 14, 19, and 20 of copending Application No. 10/471,263. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims have overlapping scopes.

The instant invention is drawn to a method of producing nuclear transfer (NT) porcine embryonic cells comprising (a) providing a porcine oocyte at the metaphase II stage of development (MetII) from which the nucleus is removed, (b) transferring a porcine karyoplast at the G0 or G1 state into said oocyte, (c) (optional step in claim 1) culturing the reconstituted embryo made by steps (a) and (b) *in vitro* to allow one or more cell divisions to give a plurality of cells in a reconstituted porcine embryo, and (d) in claim 5, thereafter transferring a plurality of porcine embryonic cells into a pregnant uterus of a female pig which at conclusion of the pregnancy gives rise to one or more genetically identical off-spring.

The copending application (claims 1, 2, and 19) more broadly claims comprising: (a) providing at least one enucleated porcine recipient cell, whose limitations can be met by a porcine oocyte at (MetII) claimed in the instant invention, (b) providing at least one porcine donor cell or nucleus, whose limitation can be met by a porcine karyoplast at the G0 or G1 state claimed in the instant invention. The instant invention more broadly claims "transferring a porcine karyoplast at the G0 or G1 state into said oocyte", whereas the copending application specifies the transfer be done by placing the enucleated recipient cell and the donor cells or nucleus in contact with one another to form couplets, providing a fusion media which is substantially free of Ca, and fusing via electrofucion to form a NT embryo. However, this more specific disclose in the copending application still encompasses the broadly claimed limitations of "transferring" in the instant applications. Claims 13, 14, and 20 of the copending application provide more specific limitations of producing cloned pig including transferring the NT embryo to synchronized females recipients, however, the more narrowly specified synchronized female recipient is encompassed by the broader limitation of transferring NT embryos to pregnant female uterus, claimed in the instant invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-7, 10, 15, and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The instant invention is drawn to a method of producing NT porcine embryonic cells comprising (a) providing a porcine oocyte at MetII from which the nucleus is removed, (b) transferring a porcine karyoplast at the G0 or G1 state into said oocyte, (c) (optional step in claim 1) culturing the reconstituted embryo made by steps (a) and (b) *in vitro* to allow one or more cell divisions to give a plurality of cells in a reconstituted porcine embryo, and (d) in claim 5, thereafter transferring a plurality of porcine embryonic cells into a pregnant uterus of a female pig which at conclusion of the pregnancy gives rise to one or more genetically identical off-spring. Narrowing embodiments specify that the cell from the reconstituted porcine embryos be synchronized at G0 or G1 and used as donor karyoblasts for a second round of NT. Narrowing embodiments also specify that G1 synchronization can be done by a DNA synthesis inhibitors, such as aphidicolin, and or microtubule inhibitors, such as nocodazole and/or by serum starvation to obtain G1 or G0. Narrowing embodiments specify that the karyoplast be treated with an agent to prevent cell division but not nuclear division to produce multiple nuclei for karyoplast. Narrowing embodiments further claim porcine embryonic cells or pigs produced by the process described above, progeny of cloned pigs and pigs produced by NT.

The specification discloses the intent of the instant invention as to provide "processes for the highly efficient production of NT porcine embryonic cells capable of high efficiency development in the pregnancy competent porcine uterine environment to give clonal infant animals." (p. 1, lines 22-24). The specification also provides methods and working examples for the production of reconstructed porcine embryos via NT. The

specification discloses a source for porcine oocytes in MetII that can be utilized for NT (p. 3, lines 13-28). Porcine somatic cells, particularly embryonic fetal fibroblast cells, are the preferred karyoplasts for the instant invention, but it was further disclosed that donor karyoplasts could also come form any porcine embryo cell, such as a totipotent blastomere, cells from a morula, or cells from the inner cell mass of blastocysts (p. 6 lines 20-25).

However, the instant invention is meant to generate porcine embryonic cells and it is not clear from the instant specification that porcine embryonic would be generated from the use of somatic cells or cell that were derived form embryos. Because a cell such as the preferred embodiment of a embryonic fetal fibroblast is transferred into an enucleated oocyte, does not make it an embryonic cell. An porcine embryo cell has certain properties, such a totipotency and the ability to generate an pig. The instant specification does not provide for methods or evidence other than cell division to demonstrate that the cells within the reconstituted embryo are embryonic cells. It has been well established in the art that the efficiency of producing NT embryos, formed with karyoplast of embryonic fetal fibroblast or embryos, that are capable of cleavage is very low. In the development of reconstituted porcine NT embryos, large numbers of NT units have to be produced to receive reconstituted embryos that further divide and further develop into recognizable embryo stages (Kuhholzer et al. Biol Reprod 64:1696 Table 2, 2001). Kuhholzer et al further discloses that cells NT units formed from various clones derived from the same primary culture of fetal fibroblast have demonstrated differing capabilities to develop in vitro (p. 1697, col 1 , par 3, lines 6-12), demonstrating

even though the cells should be similar origin they are not all necessarily going to become totipotent or demonstrate characteristics of porcine embryonic cell. It also demonstrated in the art that cells or karyoplast derived from an porcine embryo and fused with an enucleated porcine embryo with retain or have characteristics of an embryonic cell. Nagashima et al (Mol Reprod Dev 48:342, col 2, par 3, lines 1-9, 1997) discloses that the developmental ability of porcine NT embryos reconstituted with 8 to 16 cell stage nuclei cleaved at rates or 36 and 43%, respectively, and NT units reconstituted from nuclei from beyond the morula stage embryo was very low (7 and 4.5%). The further disclose that the only successful NT in pig, at the time of filing, was using karyoplast at the four-cell stage of development (p. 339, col 2, lines 11-15). These data suggest that past the early cleavage embryos (ie 2 cell to 8 cell), the differentiation state and totipotency of the embryonic cells become more and more restrictive, limiting their ability to function as an embryonic cell in NT porcine embryos.

Given that limitations to ability of a karyoplast of somatic cell or embryonic cell origin to sucessfully serve a an "embryonic cell" in an NT embryo and given that the specification provides no demonstration that the cells generated by the methods are embryonic cells, the artisans would not know how to use or make the instant invention to generate porcine embryonic cells because the artisan would not know id they were truly embryonic cells. Furthermore, an artisan would have to do further empirical experimentation to determine if the cells were true porcine embryonic cells and this level of experimentation would be considered undue.

One of the limitations of the instant method is the synchronization of the karyoplasts in G0 or G1 with the use of microtubule stabilizers, DNA synthesis inhibitors, other chemical means, and/or serum starvation. This is consistent with the NT art. Campbell et al (US Pat # 6,252,133 B1, 6/26/01) disclose the G0 or the G1 state of the karyoplast is preferred to assure the correct ploidy of the NT embryo (col 4, par 2). Others have reported that the quiescent stage of the cell cycle plays a key role in the efficiency of NT and is a requirement for reprogramming, however, others report the use of cycling, presumed G1, cells have been used sucessfully to produce offspring (Kuhholzer et al. Biol Repord 64:1697, col1 par 2, 2001). Kuhholzer et al also disclose, "The cell cycle stage is subject of debate, mainly because these is no system thus far that provides a 100% synchronization of cells in a certain stage of the cell cycle. Therefore, the use of cells in a stage of the cell cycle other than the desired one cannot be excluded. In this study, we investigated the development of porcine NT embryos derived from serum starvation (presumed G0) and cycling (presumed G1) fetal fibroblast cells. In contrast to comparative studies in cattle, in which the use of serum-starved donors resulted in better development, we found no effect of serum starvation on the in vitro development of porcine NT embryos." (p. 1697, col1 par 2). The statements of Kuhholzer et al bring into question the role of the serum starvation and other chemical means to control the stage of cell cycle in their efficacy in controlling stage of cell cycle as well as to some extend the importance of cell cycle stage in porcine NT. Ultimately it identifies an area of NT that with many unknown factors and

uncertainties in NT and the role the cell cycle as well as these techniques for controlling them in NT, that in part, adds into the unpredictability of porcine NT.

The instant invention further claims the use of NT in multiple rounds to generate more pigs. Claim 5 and the specification recites, "...culturing the nuclear transferred cell in vitro to allow one or more cell divisions to give a plurality of nuclear transferred porcine embryonic cells, and thereafter **transferring a plurality of porcine embryo cells so produced into a pregnancy competent uterus**...." (p. 2, lines 21-24). Given the broadest reasonable interpretation, this statement can suggest the transfer of the porcine embryo cells generated directly into a pregnant recipient without being present in an NT unit. There is not evidence that cells generated in an embryo can be transferred in isolation of the embryo unit and effectively produce offspring in the art. The specification provides no further support for such an approach other than the statement above, therefore is not enabled for such a method.

The instant invention further uses the porcine embryonic cells to generate cloned pigs. The working examples disclose that 9, 4, and 6 piglets were generated using the instantly claimed NT technique in three separate rounds of NT (p. 16, Table 6). However, the specification also disclose, "NT embryos were transferred into the ligated oviduct of a mated recipient the day after reconstruction to maximize development. Transferred embryos were collected 3 to 4 days later....and transferred into mated or unmated second recipients." (p. 15, lines 12-16). In reference to this, table 6 (p. 16) the 9 piglets and 4 piglets born were transferred into unmated second recipients and the litter of 6 piglets were born from a mated second recipient. Given that the first transfer

of the NT embryos were all into mated recipients and given that not marker or measure was disclosed to differentiate NT embryos from mating derived embryos, the embryos collected from the first transfers could be either NT embryos or mating derived embryos. Therefore, the pigs born could be either NT generated pigs or pigs generated by mating. Therefore, an artisan would not know if the piglets disclosed in Table 6 are truly clones. Furthermore, in post-filing art, the inventors disclose the instant methods, porcine embryonic cells, and pigs and they disclose the same data disclosing the 9, 4, and 6 piglets generated in Table 2 (Verma et al. Mol Repord Dev 57:267, 2000). They also include a microsatellite analysis of generated pigs to determine if they are clones and disclosed, "Microsatellite analysis revealed that none of these [piglets] were derived from NT transfer embryos." (p. 266, col 2, par 1, lines 9-12). These data demonstrate that their method did not generate cloned pigs by the disclosed methods.

The methods and data disclosed by the instant specification are not inconsistent with or a significantly different from methods and data reported in the art for NT in general. However, the route of the issue is that NT is still very rudimentary in nature and unpredictable. Prather et al (1999) discloses, "The technology for cloning pigs by NT is still in its infancy. Many of the techniques have been developed, but application of this technology has not met with tremendous success." (Theriogenology 51:493, Conclusions section). In theory, the known components that should function to produce a successful porcine NT and cloned pig are present in the specification and art, however there are two many unknown factors still present that make these methods that are unpredictable as seen in Verma et al (2000) and described above.

Furthermore, the specification acknowledges the many shortcoming and unpredictabilities of NT in the art. The specification states, "The reconstitution of of animal embryos by the transfer of a nucleus form a donor cell to either an enucleated oocyte or one cell zygote in theory the cloning of animal....Practice is quite different. Whilst claims have been made that certain procedures have application across a wide range of animals, experience has shown that techniques which may be effective in cloning of animals of one species with do not work in other species, give rise to embryos with very low efficiency such that cloning would be impractical, or give rise to embryos which fail to develop on introduction to a pregnancy competent uterine environment of a recipient animal." (p. 1 par 2).

Therefore, given the level of unpredictability in the art and the lack of specific guidance by the specification, an artisan would not know how to use or make the instant invention.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-7, 9, 10, 15, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims recite a/the "nuclear transferred porcine embryonic cell(s)". It is unclear if the intent of this recitation is a nuclear transfer embryo or porcine embryo cells or embryonic stem cells.

Claim 5 and the specification recites, "...culturing the nuclear transferred cell in vitro to allow one or more cell divisions to give a plurality of nuclear transferred porcine embryonic cells, and thereafter **transferring a plurality of porcine embryo cells so produced into a pregnancy competent uterus**...." (p. 2, lines 21-24). This statement can be interpreted two ways: (1) growing the cell in an NT unit and interpreting the NT unit as being the **plurality of porcine embryo cells and** transfer of the NT units, or (2) because the method in "comprising" and therefore an isolation step of the porcine embryo cells could be considered inherent, it can be interpreted as transferring isolated porcine embryo cells form the NT unit directly into a pregnant recipient without being present in an NT unit. Given these breadth of the claim and this two possible interpretation are reasonable, the metes and bound of the claim are unclear.

Claims 2, 3, 6, 7, 9, 10, 15, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recites "according to". "According" to accord is defined as the following:

1. To cause to conform or agree; bring into harmony.
2. To grant, especially as being due or appropriate: *accorded the President the proper deference.*
3. To bestow upon: *I accord you my blessing.*

http://dictionary.reference.com/search?q=according

Because "according" only implies a level of agreement with something, in the instant case other claims, the metes and bound of "according" are unclear and do not further limit the instant claims.

Regarding claim 2, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 1 recites the limitation "the nuclear transferred cell". There is insufficient antecedent basis for this limitation in the claim.

Given that all other claims dependent on 1 and 5 directly or indirectly, they are also found to be indefinite and are rejected as well.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1, 2,5-7, 9, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Campbell et al (WO 97/07668, 3/6/1997).

The instant invention is drawn to a method of producing NT porcine embryonic cells comprising (a) providing a porcine oocyte at MetII from which the nucleus is removed, (b) transferring a porcine karyoplast at the G0 or G1 state into said oocyte, (c) (optional step in claim 1) culturing the reconstituted embryo made by steps (a) and (b) *in vitro* to allow one or more cell divisions to give a plurality of cells in a reconstituted porcine embryo, and (d) in claim 5, thereafter transferring a plurality of porcine embryonic cells into a pregnant uterus of a female pig which at conclusion of the pregnancy gives rise to one or more genetically identical off-spring. Narrowing embodiments specify that the cell from the reconstituted porcine embryos be synchronized at G0 or G1 and used as donor karyoblasts for a second round of NT. Narrowing embodiments also specify that G1 synchronization can be done by a DNA synthesis inhibitors, such as aphidicolin, and or microtubule inhibitors, such as nocodazole and/or by serum starvation to obtain G1 or G0. Narrowing embodiments specify that the karyoplast be treated with an agent to prevent cell division but not nuclear division to produce multiple nuclei for karyoplast. Narrowing embodiments further claim porcine embryonic cells or pigs produced by the process described above, progeny of cloned pigs and pigs produced by NT.

Much of the embodiment of the invention is disclosed in the abstract and claims (p. 20 and 21). Campbell et al discloses methods that the NT method can be used for pigs NT and production of cloned pigs (p. 5, linesa 20-22), the the recipient oocyte is

preferable enucleated and arrested in MetII (p. 8 29-31), that karyoplast be arrested in GO or G1 (p 7, lines 15-34, to p. 8, lines 1-11), that nocodazole can be used, (p. 14, line12-14). Campbell et al discloses the instant method can be used for multiplication of genetically valuable livestock and provide uniformity in meat (p. 1 par 2) and the production of oocytes and embryos as claim in claim 18.

Claim 2 discloses multiple rounds of NT using the porcine embryonic cells generated in the first NT. Because also the step as present in the method and it is a matter of repeating them and it would be inherent the method disclosed.

8. Claims 1-4 and 15-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Prather et al (Biol Reprod 41:414-418, 1989).

The instant invention is drawn to a method of producing NT porcine embryonic cells comprising (a) providing a porcine oocyte at MetII from which the nucleus is removed, (b) transferring a porcine karyoplast at the G0 or G1 state into said oocyte, (c) (optional step in claim 1) culturing the reconstituted embryo made by steps (a) and (b) *in vitro* to allow one or more cell divisions to give a plurality of cells in a reconstituted porcine embryo. Narrowing embodiments specify that the cell from the reconstituted porcine embryos be synchronized at G0 or G1 and used as donor karyoblasts for a second round of NT. Narrowing embodiments specify that the karyoplast be treated with an agent to prevent cell division but not nuclear division to produce multiple nuclei for karyoplast. Narrowing embodiments further claim porcine embryonic cells or pigs produced by the process described above, progeny of cloned pigs and pigs produced by NT.

Prather et al disclose a cloned pig, porcine NT embryos, and porcine embryonic cells. They also disclose the use of cytochalasin B in culture of all embryos. As disclosed in the art and specification cytochalasin B results in arrested cell division but not nuclear division therefore it could be inherent to the method to produce a nuclear donor with multiple nuclei. Furthermore, as discussed above, claim 2 discloses multiple rounds of NT using the porcine embryonic cells generated in the first NT. Because also the step as present in the method and it is a matter of repeating them and it would be inherent the method disclosed.

9. Claim 18 rejected under 35 U.S.C. 102(e) as being anticipated by Stice et al (Pat # 5,945,577, filing date 1/10/1997).

Claim 18 recites the use of cloned pigs for organ production.

Stice et al. disclose the production of pig NT units for cloning [86] and disclose the production of organs for transplantation [112].

10. Claims 15 and 18 rejected under 35 U.S.C. 102(e) as being anticipated by Wheeler (US Pat # 5,942,435 8/24/1999, fd-6/6/1995).

Claim 15 recites porcine embryonic cells and claim 18 recites embryo production.

Wheeler discloses the production of porcine embryonic stem cells and methods for making embryos with these cells (col 4 lines 23-48).

11. Claims 15-17 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Cisneros et al (1996) J. Animal Science 74, 925-933.

The claims are drawn to pig offspring and progeny produced by claimed methods of cloning a mammal. However, as claims 15-18 are product, a teaching of the same

products obtained by a different method serves as anticipatory art against the instantly rejected claims. There is no language in claims 15-18 which provides any patentable distinction over the pig offspring and progeny in the art.

Cisneros et al teach a commercial pig breed, BCH, and a three breed cross, HYD, (page 926, col. 1, parag. 1, lines 4-6). These pigs inherently are progeny and offspring of parental crosses. Without a distinction which indicates a structural or functional difference between the claimed offspring and progeny and those disclosed in Cisneros et al, then Cisneros et al anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell et al (WO 97/07668, 3/6/1997) and Tsunoda and Kato (J Reprod Fert 113(2):181-184, 7/1998).

Campbell et al disclose the method in general as described above but does not disclose specifically the use of aphidicolin. Campbell also provides the motivation to use such agents to assure proper ploidy of the embryo as described above.

Tsunoda and Kato discloses the use of aphidicolin in producing mouse NT embryos (see abstract) but does not teach porcine.

It would be obvious to an artisan to use aphicolin as described in Tsunoda and Kato in porcine NT as disclosed by Campbell et al. Campbell et al provides the motivation to use agents as aphicolin for assuring proper ploid of the NT unit. Therefore more an artisan would combine these methods with a reasonable expectation of success because aphicolin arrests DNA synthesis therefore promoting G1 state of the karyoplast and because it has been sucessfully used in other NT method. Furthermore, it must be noted that aphicolin use provides no novelty to the instant invention, nor does it enable the instant invention.

13. Although claims 8, and 11-14 are withdrawn and for the sake of compact and expeditious prosecution, it is noted that these claims are anticipated by Campbell et al (WO 97/07668, 3/6/1997), which discloses multiple DC electric pulses ub activation can be used (p. 3, lines 18-30).

14. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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